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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,788	04/20/2007	Valerio Berdini	3073.006B	2889

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HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY, NY 12203

EXAMINER	
WEST, THEODORE R	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
10/03/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,788	BERDINI ET AL.	
	Examiner	Art Unit	
	Theodore R. West	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *76-108* is/are pending in the application.

5a) Of the above claim(s) *81-85,93 and 105-108* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *76-80,86-92,94-104* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

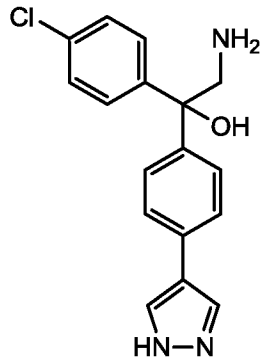
DETAILED ACTION

Applicant's amendment submitted on August 8, 2011 has been entered. Claims 81-85 and 93 are withdrawn as being drawn to a nonelected species. Claims 105-108 are withdrawn as being drawn to a nonelected invention. Claims 76-80, 86-92, and 94-104 are rejected for the reasons set forth below.

Election/Restrictions

Applicant's election without traverse of the invention of Group I, drawn to compounds of formula (I) and compositions thereof, in the reply filed on August 8, 2011 is acknowledged. Currently, claims 76-104 correspond to Group I. Claims 105-108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Applicant's election without traverse of the following species for initial examination in the reply filed on August 8, 2011 is acknowledged: 2-amino-1-(4-chloro-phenyl)-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol, which is disclosed as Example 84 on page 181 of the specification and is illustrated below:



Claims 76-80, 86-92, and 94-104 read on the elected species. Claims 81-85 and 93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse. The elected species is not allowable. During the course of examination, certain prior art that pertains to nonelected species was found, and in the interest of advancing prosecution of the application it has been applied to the appropriate claims (including withdrawn claims, if appropriate) as discussed below. The prior art search, however, has not be extended unnecessarily to cover all nonelected species, and the requirement for a species election has not been withdrawn because the claims include subject matter that has not been searched. See MPEP § 803.02.

Claim Rejections - 35 USC § 112, Second Paragraph

Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76-101 and 103-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I) wherein R^1 is a benzene or a pyridine and E is also a benzene or a pyridine, does not reasonably provide enablement for the other claimed R^1 and E groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered when determining whether claims in an application for patent are enabling include (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). See also, MPEP § 2164. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the full scope of the claimed invention without undue experimentation. A discussion of these factors as they relate to the pending claims follows.

(1) The breadth of the claims and (2) the nature of the invention

The claims are directed to compounds of formula (I), which applicant's specification asserts are useful as protein kinase A ("PKA") and protein kinase B ("PKB") inhibitors (see specification at p. 1, ll. 3-9). In the generic chemical structure of formula (I), the R^1 group may be essentially any aromatic or heteroaromatic group, and

the E group may be essentially any carbocyclic or heterocyclic group, and therefore the claimed generic chemical structure is broad.

(3) The state of the art

The pharmacology of PKA inhibitors is known in the art to be unpredictable and complicated. For example, "Pharmacological PKA Inhibition: All May Not Be What It Seems" by Murray, Sci. Signal. 1, re4 (2008) discloses that transduction of extracellular signals to intracellular responses through a PKA pathway is one of the most important and complicated aspects of cellular life (p. 1, left column). In fact, a number of studies have identified widespread actions of PKA inhibitors that are independent of their effects on PKA, and they include actions on other protein kinases and signaling molecules and also on basic cellular functions such as transcription (see Abstract). Competition for ATP binding on protein kinases is a mechanism commonly exploited in developing pharmacological PKA inhibitors; however, this approach presents a number of distinct and important problems (p. 1, right column). First, the IC_{50} values of PKA inhibitors vary according to the ATP concentration; and because ATP concentrations vary widely in cells depending on the prevailing physiological conditions, the concentration of inhibitor required for effective protein kinase blockade is not always clear (p. 2, left column). Second, various nonspecific effects of PKA inhibitors have been reported (p. 2, center column). These side effects of PKA inhibitors are extremely varied; some of the most worrisome actions are the substantial effects on the MAPK and calcium signaling pathways, which interact with the PKA pathway and mediate multiple cellular functions

(p. 5, center column). The prior art therefore indicates that in vitro activity is not necessarily predictive of in vivo utility.

The pharmacology of PKB inhibitors is also known in the art to be unpredictable and complicated. For example, "A comprehensive structure-activity analysis of protein kinase B-alpha (Akt1) inhibitors" by Ajmani et al., J. Molec. Graph. Model. 28, 683-94 (2010) discloses that an analysis of a wide variety of structurally diverse PKB (also known as Akt1) inhibitors collected from various literature reports reveals that the topological descriptors of the compounds are important for their biological activity (p. 693, left column). For example, the number of hydrogen bond acceptors, number of hydrogen bond donors, number of rotatable bonds, molecular branching, number of aromatic oxygen, and alkene carbon atom type all contribute to PKB inhibition activity (p. 693, left column). Some molecular features are known to have highly dominant effects on the activity of inhibitors, whereas other molecule fragments are less important in governing activity variation (p. 693, left column). In addition, analyses shows that chemical variations such as the presence of heteroaromatic rings, flexibility, polar surface area, fragment length, etc. at the highly dominant fragments are critical for achieving highly potent kinase inhibitors (p. 693, left column). These important fragment features can form the building blocks to design new molecules with their corresponding highlighted features being optimized (p. 693, left column). The prior art therefore teaches that the activity of a PKB inhibitor is highly dependent on its chemical structure.

Finally, the synthesis of new chemical compounds is highly unpredictable. For example, "Organic Synthesis: General Remarks" in Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design by Dorwald, Wiley-VCH (Weinheim, Germany), Preface and p. 1 (2005) discloses that most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are (see Preface). The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why (Preface). Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task (Preface). In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization (Preface). The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence (Preface). Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work (Preface). Organic reactions almost never yield exclusively the desired product, which students learn upon performing their first synthesis in the laboratory (p. 1). Because most reactions yield by-products and because isolation and purification of the desired product

are usually the most difficult parts of a preparation, the workup of each reaction and the separation of the product from by-products and reagents must be carefully considered while planning a synthesis (p. 1). Many small molecule compound that appear, at least on paper, to be easy to prepare are still unknown, not because nobody has attempted to make them, but because isolation and purification of such compounds can be very difficult (p. 1). Thus, the art recognizes that the synthesis of new chemical compounds is a very difficult, inefficient, labor-intensive, process known to be plagued by many failures and frustrations.

(4) The level of one of ordinary skill

One of ordinary skill in the art is a person having advanced training or other significant relevant experience in medicine, pharmacology, chemistry, or another related technical discipline.

(5) The level of predictability in the art

Pharmacology, chemical reactions, and physiological activity are generally regarded as being unpredictable sciences. See MPEP § 2164.03. The evidence presented above demonstrates that the pharmacology of PKA/PKB inhibitors is known to be unpredictable. The activities of such kinase inhibitors are known to be highly dependent on their chemical structures, which include features that are “critical” to their function. Some examples of critical chemical features include the number of hydrogen bond acceptors/ donors, molecular branching and rotatable bonds, the presence of or absence of heteroaromatic rings, and so forth. It is further known in the art that protein kinase pathways are complicated aspects of cellular life, and that in vivo attempts to

inhibit protein kinases are associated with a number of distinct and important unsolved problems. Finally, the prior art discloses that synthetic organic chemistry is difficult, unpredictable, inefficient, labor-intensive, and replete with unexpected difficulties, failures, and frustrations.

(6) The amount of direction provided by the inventor and (7) the existence of working examples

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. The less predictable the nature of the invention, the more information needs to be explicitly stated in the specification. See MPEP § 2164.03.

Applicant's specification provides working examples illustrating the synthesis of compounds in which R^1 and E are both benzene (see, generally, Examples 1-105 at pp. 105-97). Some of the compounds have a pyridine as the R^1 group (see, e.g., Example 19 at p. 122), and some of the compounds have a pyridine as the E group (see, e.g., Example 60 at pp. 150-57). There are no working examples of compounds having any R^1 or E groups other than benzene or pyridine. The working examples do, however, have a wide range of different R^2-R^5 substituents (see, e.g., Examples 1-105 at pp. 105-97). The working examples include data (see Examples 106-107 at pp. 197-99) demonstrating that the compounds have in vitro utility in inhibiting both PKA and PKB.

The specification also provides a general discussion (see Schemes 1-10 at pp. 62-86) about how compounds having various different R^1 and E groups may be

synthesized, but there is no indication that these synthesis schemes actually work as illustrated or that they have been reduced to practice.

(8) The quantity of experimentation needed

In order to practice the invention commensurate with the scope of the claims, the skilled artisan would need to undertake extensive and undue experimentation.

There is no evidence of record that the kinase-inhibiting activity of a given compound, especially compounds wherein R^1 and E are not benzene or pyridine groups, can be readily predicted. In fact, the evidence suggests that changing these groups, which constitute significant portions of the core chemical structures of the working examples in the specification, would reasonably be predicted to negatively alter or destroy the kinase inhibiting activity of the compounds. That is, it appears to be critical that the R^1 and E groups be either benzene or pyridine.

In addition, the skilled artisan will need to experimentally determine how to synthesize compounds in which the R^1 and E groups are not benzene or pyridine. The prior art discloses that small molecule compounds that appear, at least on paper, easy to synthesize are nevertheless expected to require extensive experimentation to actually prepare.

Conclusion

Because of the unpredictability of whether compounds in which R^1 and E groups be not benzene or pyridine will actually be useful as PKA/PKB inhibitors, and because of the unpredictability in the synthesis of such compounds, it is the examiner's position

that the claims are only enabled for compounds in which R^1 is a benzene or a pyridine and E is also a benzene or a pyridine.

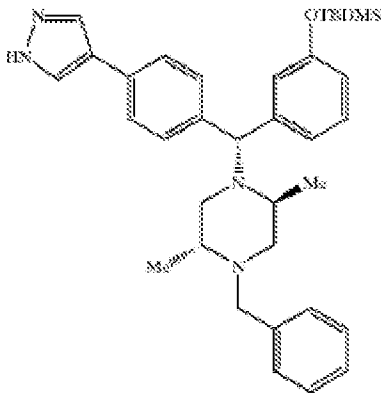
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 76-79, 89-92, 101, and 103-104 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,200,978 B1 by Maw et al.

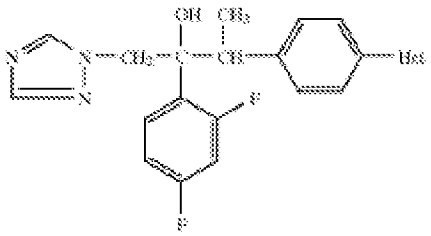
Maw et al. discloses the following compound:



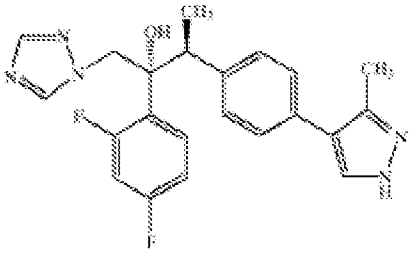
(see "Preparation 48" at col. 119, ll. 5-20). This is a compound according to formula (I), wherein A is a C_1 hydrocarbon linker, R^1 is a substituted benzene, R^2 and R^3 together form a heterocyclic group, R^4 and R^5 are both hydrogen, and E is a benzene. The compound may be in the form of a salt and it may be formulated as a pharmaceutical composition with a carrier (col. 3, ll. 56-67).

Claims 76-78, 89-91, 101, and 103-104 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,015,825 by Bell et al.

Bell et al. discloses the following compounds:



, wherein "het" is a pyrazole, and



(see Example 39 at col. 29 and Example 98 at col. 71, respectively). They are compounds according to formula (I), wherein A is a C_4 hydrocarbon linker substituted with a hydroxyl group, R^1 is a substituted benzene, R^2 and R^3 together form a heterocyclic group, R^4 is hydrogen, R^5 is either a hydrogen (Example 39) or a C_1 hydrocarbon, i.e., methyl (Example 98), and E is a benzene. The compounds may be in the form of salts (col. 3, ll. 16-26) and they may be formulated as pharmaceutical compositions with a carrier (col. 16, ll. 1-3).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obvious-ness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 76-80, 86-92, and 94-104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 63-87 of copending Application No. 12/531,013. Although the conflicting

claims are not identical, they are not patentably distinct from each other. The claims of the '013 application specifically claim applicant's elected species (see, e.g., claim 63) and compositions thereof (see, e.g., claim 69).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 76-104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 131-155 of copending Application No. 11/993,823. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '823 application claim compositions comprising compounds of formula (I) (see, e.g., claim 131), as well as applicant's elected species (see, e.g., claim 146).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 76-104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 91-114 of copending Application No. 11/993,831. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '831 application claim methods of using compounds of formula (I) (see, e.g., claim 91), as well as applicant's elected species (see, e.g., claim 108).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Correspondence Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Theodore R. West whose telephone number is (571)270-5993. The examiner can normally be reached on Monday to Friday, 10:30 am to 7:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon J. Fetterolf can be reached on (571)272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/T. R. W./
Examiner, Art Unit 1628

/Anish Gupta/
Primary Examiner, Art Unit 1654